ON AMORPHOUS QUININE.

Medicinal Value of Cinchona Bark.

It is now above two hundred years since the extraordinary powers of certain barks — the produce of South America — to control and cure fevers, and to restore tone to the human constitution when debilitated by certain diseases, have been known to medical men. During that long period, and amid numberless revolutions in pathological doctrines, these barks had been constantly employed, and their use has increased and extended over all parts of the world.

The possession of a remedy for the various forms of fever, indigenous to every climate where marshy soils or wooded tracts exist, has been one of the main causes of the extension of commerce and the spread of civilization. Whilst in new countries, or in partially cultivated districts of the old, fevers are always prevalent, either in numerous sporadic cases or as frequently recurring epidemics, there is scarcely a locality, either of town or country, where similar fevers, or other diseases, arising from imperfect draining or insufficient ventilation, are not daily met with. Every variety of fever having a marked periodicity,—a time of remission and exacerbation,—and a great variety of morbid conditions, such as neuralgia, hemicrania, &c., seem to be remediable by the employment of some form or other of the cinchona barks.

Discovery of Quinine.

The discovery of Pelletier and Caventou in 1820, that the antiperiodic therapeutic efficacy of bark resides in a separable principle, having the property of combining with acids and forming salts, by making the administration of the remedy more easy and agreeable, greatly extended its application, and increased the commercial demand. The importation of bark and the manufacture of quinine form considerable items in the commercial industry of this country.

The use of the alkaloid in its pure state is scarcely generally known in practice, nor are there many combinations at present employed. The convenience of the manufacturer, as much as any other cause, has led to the adoption of the *Sulphate of Quinine* in practice, and this is now almost the only form under which it is employed, or in which it is to be generally obtained in commerce. Of the quantity of this medicine consumed, an idea may be formed, when we find it stated that 120,000 ounces of sulphate of quinine are manufactured annually in Paris alone. But England, Italy, Germany, and America have all their makers of sulphate of quinine.

Value of the Sulphate of Quinine.

Although in every pharmacy in the world, and in daily use every where, it has been considered by many eminent practitioners, that, valuable as the *crystalline* sulphate of quinine undoubtedly is, it does not fulfil every condition required in practice for employing the remedial properties of bark, and in some cases inconveniences are experienced from its use, which it would be well, when possible, to avoid. These circumstances lead many persons, even at the present day, and in spite of the woody fibre and nauseous taste, to administer the bark in substance, or to prefer an infusion or decoction, notwithstanding the vagueness and uncertainty of these preparations.

Uncrystalline Bodies more congenial to the Animal Economy than Crystalline.

From certain recent investigations and experiments, it appears that all the objections found in practice to the common sulphate of quinine, may possibly depend simply on its *crystalline* form.

Every physiologist knows that crystalline bodies are apt to escape decomposition in the stomach, being as Dr. Prout has well observed, "the form in which substances are farthest removed from organization and life." In accordance with this view, chemists have often observed that the crystalline sulphate of quinine is found undecomposed in the patients' urine. Simple infusion and decoction of bark, which have commonly been resorted to, have many elements of uncertainty.

Compounds of Quinine with Vegetable Acids.

From numberless analogies, it would appear to be in the highest degree probable that combinations of quinine with vegetable acids would be in some cases preferable; these acids decomposing in the system, and thus presenting the alkaloid to the organism in a nascent state. In America, where intermittent and remittent fevers in every possible variety of form and degree of severity abound, infusions of bark in weak vegetable acids have been employed, and it appears with admirable effect; these being said to be more efficacious than watery or spirituous infusions, or than the *crystalline* sulphate of quinine, the

only salt with which the American practitioners have had the opportunity of comparing these acid infusions. In Italy the acetate has been used with success, and this appears to represent the class of organic acids.

Discovery of an Uncrystalline Quinine.

In 1829-30, Dr. Sertuerner published several papers in "Hufeland's Journal" on the Nature and Treatment of Intermittent Fevers, and also a separate work in 3 vols. on the same subject. In 1828, an intermittent had been epidemic in his neighbourhood, and he tells us he found himself frequently disappointed in the use of sulphate of quinine, which he became perfectly sure does not represent the whole therapeutic efficacy of the peruvian bark. Dr. Sertuerner then turned his attention to a chemical investigation of the bark itself, and first he endeavoured to ascertain what was left behind in the liquors extracted from the bark, and from which after the addition of sulphuric acid the sulphate of quinine is crystallised. He soon found in these mother-liquors a substance having all the properties of an organic alkaloid, but which *he was not able to crystallise.* This substance he immediately subjected to experiments to test its therapeutic effects, especially in intermittent fevers, and the result was, he assures us, that it is preferable to ordinary sulphate of quinine or the bark in substance, even when he gave it in less doses than the sulphate. In a great number of cases where other remedies failed, he found his supposed new alkaloid succeed, and he therefore began to use it in all cases of intermittent fevers, and those numberless forms of disorder caused by malaria.

His success was so satisfactory that he pronounces it "a true fever-destroyer," and is satisfied that, beyond all other substances, it deserves the title of *febrifuge.*

Many other writers bear similar testimony to the effects of Sertuerner's supposed new alkaloid, which became a subject of inquiry with many German physicians and chemists. Winkler, as quoted by Berzelius, threw out the suggestion that Sertuerner's alkaloid appeared to be simply the quinine itself—but he could not crystallize its salts; and Berzelius adds, that the subject required elucidation.

This it has lately received from the profound sagacity and skill of Baron Liebig, who writes of it as follows:—

"On Amorphous Quinine, as it exists in the substance known in commerce as Quinoidine.

"In the preparation of sulphate of quinine, after all the crystals which can be obtained are separated, a dark-coloured mother-liquor remains, having an extremely bitter taste. On the addition of an alkaline carbonate, this liquid loses its colour and bitter taste, depositing, at the same time, a yellowish-white, or brownish precipitate, which, after being rinsed with water, and exposed to a gentle heat, agglutinates into a coherent mass, exhibiting the appearance of resin.

"From the experiments of Sertuerner, Thiele, Bucholz junior,

Koch, and other chemists, it has been long known that this resinous substance possesses the properties of a base, that it neutralizes acids perfectly; but the salts which are formed by these combinations with acids have baffled all attempts at crystallization.

"Sertuerner, who was the first chemist to separate this resinous substance from the mother-liquor of sulphate of quinine, considered it to be a distinct and peculiar organic base, existing in yellow and red cinchona barks, associated with quinine and cinchonine. He assigned to this, as he supposed, new substance, the name Quinoidine, and greatly extolled its medicinal efficacy, in which he declared it was in all respects equal to quinine. In his journal, ('Uber die neuester Furtschritte in der Chemie, Physik und Heilkunde,' Bd. iii. No. 2, page 269,) he terms it 'a true fever-destroyer.'

"Subsequently, this substance, under the term Quinoidine, has been employed medicinally in many places, and even introduced into the lists of commercial articles or price currents of many of the druggists of Germany.

"In certain mother-liquors of quinine left in the preparation of the sulphate, which were analyzed by Henry and Delondre, and also a sample of quinoidine examined by Geiger, these able chemists discovered an amount of quinine and cinchonine, accompanied by a resinous substance which they considered impeded the crystallization of the sulphates of the two bases, and which in their experiments they failed to separate. The results obtained by these chemists, and the inferences obviously deducible from these results, rendered it indubitable that the medicinal efficacy of quinoidine must vary according to the greater or less proportion of quinine it may happen to contain. Now, there cannot be a doubt but that this uncertainty with respect to the relative amount of quinine in commercial quinoidine, has prevented many physicians from prescribing the latter as a remedy, notwithstanding the testimony borne to its efficacy.

"Having occasion, some time since, to pass through Coblentz, I procured from Messrs. Jobst and Co. of that town, a sample of quinoidine, for the purpose of employing it for the preparation of Quinoleine—a substance discovered by Gerhardt to result from the transformation of quinine, and to which much scientific interest attaches, in consequence of the recent discovery of Professor A. W. Hofmann, that quinoleine is identical with leucol, a body which is one of the components of the essential oil of tar, prepared from anthracite coal. It then occurred to me, that if the sample of quinoidine which I had procured contained quinine, it must yield a corresponding amount of quinoleine, and that, consequently, a very simple method of testing quinoidine for the amount of quinine it may contain might be based upon this property of quinine to be transformed into quinoleine.

"On subjecting the sample I had obtained (which amounted to several ounces) to distillation with strong potass ley, I confess I was surprised at the large amount of quinoleine produced, which proved the presence of a far larger proportion of quinine than could have been anticipated. This unexpected result induced me to subject quinoidine to a stricter examination; and in order to avoid being misled by accidental circumstances, I procured, beside the Coblentz sample, specimens

from Messrs. Hess, Leissler, and Fiedler, of Mayence; and from Messrs. Mettenheimer and Simon, at Frankfort; and also from a druggist at Hamburg.

"These various samples of quinoidine I received partly in irregularly-shaped masses, and partly as square cakes of a darker or lighter brown colour, which, by the warmth of the hand, became soft and flexible, but were readily pulverisable in the cold. The operation of powdering it imparted to it an extraordinary degree of elasticity. All these samples were completely insoluble in cold water, but scantily soluble in hot water, imparting to the latter a strongly bitter taste. I may here, however, observe, in passing, that some commercial specimens which I have since seen are soluble in cold water, arising from a considerable admixture of other substances; differing also, from the same cause, in many of the following properties:

"All the first samples I speak of dissolved in alcohol, in the proportion of one part to two of menstruum; and from this alcoholic solution water precipitates copious, yellowish-white, resinous flakes, which cohere into a mass like the original quinoidine. Dilute mineral acids, as well as most of the organic acids, dissolved my samples entirely, and by adding a sufficient amount of the substance, became completely neutralized. From these solutions in acids, ammonia and alkaline carbonates precipitated resinous flakes. On agitating the fluid containing these flakes and the flocculent precipitate with an equal volume of ether, the precipitate dissolves in the ether, *with the exception of a dark-brown residue.* On evaporating the ether, a resinous mass is obtained, having all the properties of an organic alkaloid.

"Its salts are precipitated by tannic acid. Chloride of platinum produces in its solution in hydrochloric acid a yellow precipitate. Moreover, it dissolves completely in a solution of sulphate of copper with the separation of oxide of copper. Now there exists no resin, nor, indeed, any other substance similar to resin, which possesses this peculiar property.

"These observations can leave no doubt whatever as to the chemical character of a considerable proportion of the residue to which the term quinoidine has been applied—namely, that it is a true organic base.

"On subjecting the purified substance to elementary analysis, it is proved, beyond the possibility of error, that this organic base is nothing more nor less than quinine itself in an AMORPHOUS or uncrystalline state. The uncrystalline substance derived from quinoidine bears exactly the same relation to ordinary quinine that uncrystalline sugar (barley-sugar) bears to crystalline (sugar-candy). Both yield the same products of decomposition; both have the same atomic weight, and identically the same composition; they differ only in form: in one word, the one is crystalline, the other, *amorphous.*

"I deem this to be an important discovery, when we consider the high price of quinine, the possibility of a check to the supply of cinchona bark from the countries producing it, and the amount of the crude quinoidine which has accumulated since the manufacture of sulphate of quinine was commenced. Quinine, indeed, seems to be absolutely indispensable for the treatment of diseases; the progress of

civilization in modern times has depended, far more than has been conceived, upon the discovery of a remedy for the fevers which prevail where tillage is imperfect, and in new and unbroken soils.

"This chemical investigation has thrown an interesting light upon the testimonies borne to the efficacy of quinoidine in the treatment of fever, and the highest encomiums have been passed upon it; but the commercial specimens have differed very much in value; while some have consisted nearly altogether of amorphous quinine, others have contained only a small per centage."

There cannot be a doubt entertained but that amorphous quinine will come into general use, not merely as a substitute for, but as a preparation of quinine, superior in efficacy to the alkaloid in a crystalline form; in the amorphous condtion it appears to be more congenial to the system, more easily assimilated, and produces its effects with more certainty.

In order to ensure completely the utmost convenience in prescribing and administering the amorphous quinine, two of its salts — one, that of an inorganic, the other that of an organic acid—have been selected and prepared in solution, namely,—

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